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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/712,124	11/13/2003	Victoria Smith	P2000R1	7683

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EXAMINER	
QIAN, CELINE X	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/712,124	SMITH, VICTORIA	
	Examiner	Art Unit	
	Celine X. Qian Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *31-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0205,0705*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-45 are pending in the application.

Election/Restrictions

Applicant's election of Group I in the reply filed on 10/27/06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Accordingly, claims 31-45 are withdrawn from consideration for being directed non-elected subject matter. Claims 1-30 which is directed to SEQ ID NO: 3, 13, 17, 23 and 43 are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description requirement is set forth by 35 U.S.C. 112, first paragraph which states that the: "*specification* shall contain a written description of the invention. . .[emphasis added]." The written description requirement has been well established and characterized in the case law. A specification must convey to one of skill in the art that "as of the filing date sought,

[the inventor] was in possession of the invention." See *Vas Cath v. Mahurkar* 935 F.2d 1555, 1560 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Applicant may show that he is in "possession" of the invention claimed by describing the invention with all of its claimed limitations "by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention." See *Lockwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

In analyzing whether the written description requirement is met, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. The claims recite variants of AGR2, TM7SF1, MAT2B, SLNAC1 and TCF4. The claimed genus is broad because it encompasses nucleic acid or amino acid sequences that are homologous to each of the individual genes or polypeptides or proteins that have same function as said genes. However, the specification only discloses measuring expression of the recited genes in esophageal tissue sample in patients, but not other variants as recited. As such, in the context of measuring HGD by measuring gene expression, the specification fails to disclose a structural functional relationship between the claimed variants and their expression relative to the indication of HGD. The specification also fails to disclose a correlation between the expression of the claimed variants and HGD. Therefore, the written description requirement is not met.

Claims 1-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in

the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

The nature of the invention:

The claims are drawn to a method of detecting high grade dysplasia or determining predisposition to a neo-plastic transformation by measuring gene or protein expression of five genes: AGR2, TM7SF1, MAT2B, SLNAC1 and TCF4.

The teaching of the specification and the breadth of the claim:

The specification discloses in working examples of measuring differential gene expression in patients suffering from Barrett's esophagus, dysplasia and carcinoma. The specification discloses genes that have differential expression in different stages of the above disease progression. With respect to five gene claimed, the specification discloses that the expression of TCF4 and AGR2 are elevated in esophageal high grade dysplasia (see Figures 2A and 3A), and SLNAC1, TM7SF1, MAT2B and AGR2 are elevated in intestinal metaplasia (see Table 2). The claim breadth is broad since it is directed to a method of detecting all types of

high grade dysplasia regardless of its tissue origin by monitoring the expression of the recited 5 genes in any type of mammal. The specification fails to disclose whether elevated expression of the combination of said genes is indicative of any type of dysplasia in any type of mammal. Thus, the disclosure of the instant specification is limited with regard to the claimed scope.

State of the Art & Predictability of the Art:

The prior art teaches that there are many factors that need to be considered in order to develop a reliable genetic test. Shalon et al (US 2001/0051344 AI, Dec 13, 2001) teach that due to variations in genetic make-up of unrelated individuals in a heterogeneous society, differences in the expression of a gene between any two individuals may or may not be significant (see page 10, paragraph [0155]). Shalon et al further teach that the larger the number of individuals tested, the more significant the remaining differences in gene expression become and samples from at least 5 and preferably 20-50 different test individuals are assayed to obtain statistically meaningful data showing a statistical elevation or reduction in report levels when compared to control levels (see page 10, paragraph [0156]). Shalon et al teach that the test average pattern is compared with a control average pattern on a microarray to identify test genes which show significantly, typically at least 2 fold and up to 100 fold or more, increase or decrease in gene expression level with respect to control levels for the same gene (see page 10, paragraph [0158]). Kroese et al (Genetics in Medicine 6(6) :475-480, 2004) teach genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined. Kroese et al teach that a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods. (e.g. page 476, 2nd column, last paragraph). Kroese et al teach that genetic

test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (e.g. page 477, 1st column, 1st and 2nd full paragraph). Kroese et al teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests (e.g. page 479, 2nd column, last paragraph). Additional prior art reveals that most gene association studies are typically wrong. Lucentini (The Scientist, 18(24):20, 2004) teaches that it strikingly common for follow-up studies to find gene-disease associations wrong (e.g. page 3, 2nd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to complex disease there is only roughly a one-third chance that the study will reliably confirm the finding (e.g. page 3, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revised statistical methods, should be included in the gene association studies (e.g. page 4, 2nd paragraph).

Thus, the state of the prior art was underdeveloped and unpredictable at the time of Applicant's filing. In the instant case, the issue is further complicated by the fact that the claims encompass genes of various function and are involved in different diseases. For example, AGR2 is over-expressed in prostate cancer (Zhang et al., Genes, Chromosomes & Cancer, 2005, Vol.43, pages 249-259), whereas TCF7L2 is associated with type 2 diabetes (Diabetes, Vol 55, pages 2903-2908, 2006). As such, the recited genes may have elevated expression due to different

causes than that is correlated with high grade dysplasia. Furthermore, whether the elevated expression of the claimed genes in intestinal metaplasia and esophageal dysplasia can extend the predictability to dysplasia of other tissue origin is unpredictable.

Amount of Experimentation Necessary:

Given the underdeveloped state of the art and the level of unpredictability in the art, one of ordinary skill in the art would have been required to perform an undue amount of experimentation in order to first, accurately determine gene expression differences in colon and esophageal tissue of patients with high grade dysplasia of said tissue only (and without other disease) and normal tissue. Then, one of skilled in the art would have to determine which of those differences were indeed indicative of the disease and could therefore be used in the detection of the disease. The skilled artisan would also have to determine whether elevated expression of the five genes in esophageal and colon tissue is indicative of HGD in other tissues. This amount of experimentation is exacerbated by the large breadth of the claims would require the skilled artisan to perform undue experimentation to practice the method as claimed. Therefore, the claimed invention is not enabled by the instant specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 10, 14-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 3, the recitation of "comprising detecting esophageal HGD in a test tissue sample according to claim 1" renders the claim indefinite because it is unclear whether it is a "a method according to claim 1" or "a test tissue sample according to claim 1."

Regarding claim 10, the recitation of "at least eight polypeptides" lack antecedent basis because claim 9 only recites 5 polypeptides.

Regarding claims 14-24, the recitation of "at least eight/ten/twelve/fifteen/...genes from the group" renders the claim indefinite because it lacks antecedent basis (claim 13 only recites 5 polypeptides). Further, the recitation of "from a gene selected from the group" also renders the claim indefinite because it is unclear how five-gene expression can be detected with a nucleic acid from only one gene.

Regarding claim 25, the recitation of "a probe comprising at least 50 contiguous nucleotide from a gene selected from the group to nucleic acid of cells of test tissue sample relative to cells of normal tissue control" renders the claim indefinite because it is unclear how the hybridization to test sample is determined by relative to control sample. Further, it is unclear how five-gene expression can be detected with a nucleic acid from only one gene. Claims 26 and 27 are rejected because they depend on claim 25.

Regarding claim 3, the recitation of "comprising detecting esophageal HGD in a test tissue sample according to claim 1" renders the claim indefinite because it is unclear whether it is a "a method according to claim 1" or "a test tissue sample according to claim 1."

Regarding claim 10, the recitation of "at least eight polypeptides" lack antecedent basis because claim 9 only recites 5 polypeptides.

Regarding claims 14-24, the recitation of "at least eight/ten/twelve/fifteen/...genes from the group" renders the claim indefinite because it lacks antecedent basis (claim 13 only recites 5 polypeptides). Further, the recitation of "from a gene selected from the group" also renders the claim indefinite because it is unclear how five-gene expression can be detected with a nucleic acid from only one gene.

Regarding claim 25, the recitation of "a probe comprising at least 50 contiguous nucleotide from a gene selected from the group to nucleic acid of cells of test tissue sample relative to cells of normal tissue control" renders the claim indefinite because it is unclear how the hybridization to test sample is determined by relative to control sample. Further, it is unclear how five-gene expression can be detected with a nucleic acid from only one gene. Claims 26 and 27 are rejected because they depend on claim 25.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X. Qian Ph.D. whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Celine X Qian Ph.D.
Examiner
Art Unit 1636

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PRIMARY EXAMINER